REMARKS

Status of the Claims

Claims 12-17 and 24-35 are pending in this application. Claims 1-11 and 18-23 are canceled.

Information Disclosure Statement

Applicants submitted an Information Disclosure Statement on July 16, 2007. Applicants request that the references cited therein be considered by the Examiner.

Support for Amendments

Claim 12 is amended to remove the term "about" from line 2 of the claim. Support for the amended claim can be found in the specification as filed, for example at page 13, lines 14-21.

Claims 14 and 25 are amended to indicate that a preferred embodiment is a 3-4 week cycle. Support for the amended claim can be found in the specification as filed, for example on page 12, lines 1-3.

No new matter is added.

Foreign Priority

The present application is a national phase application of PCT patent application PCT/GB00/01857, filed May 15, 2000 and claims priority to:

(1) GB 9911183.3, filed May 13, 1999,

(2) GB 9911346.6, filed May 14, 1999,

(3) GB 9927005.0, filed November 15, 1999,

(4) GB 9918534.0, filed August 5, 1999,

(5) GB 9927106.6, filed November 16, 1999, and

(6) GB 0007637.2, filed March 29, 2000.

The Examiner has withdrawn the prior acknowledgment of Applicants' claim of priority to these foreign applications and determined that the earliest effective filing date for the currently pending claims is May 15, 2000. In particular, the Examiner contends that there is no clear support in the foreign applications for the limitation "at a dose level of about 500 to about 1650 micrograms/m^2 body surface area" added to claim 12. Applicants respectfully traverse this position.

Applicants note that GB 9911183.3, filed May 13, 1999 includes an Example disclosing that 10 patients received a dose of 1500 $\mu g/m^2$ of Et 743 as a 24 hour continuous infusion every three weeks, with two partial responses, two minor responses, and three stabilizations. In addition, GB 9911346.6, filed May 14, 1999 includes an Example disclosing that patients received doses of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour continuous infusions, and partial responses, a minor response, and stabilizations were observed. Therefore, at least claims 27-29 are entitled to the priority dates of GB 9911183.3 and GB 9911346.6.

With regard to GB 9918534.0, filed August 5, 1999, the disclosure indicates infusion times of up to 24 hours, 2-12 hours, 12-24 hours, and 3 hours are disclosed on page 2. Intervals of 2 to 4 weeks are disclosed on page 2. In one example, 11 patients were treated at a dose of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour infusions, and another patient was treated at a dose of 1500 $\mu g/m^2$ of Et 743 during a 3 hour infusion. Six partial responses, one minor response, and 4 stabilizations were observed. In another example (on the page entitled "A Phase I and Pharmacokinetic (PK) study of ET-743 evaluating a 3 hours (h) intravenous (iv) infusion

(T) in patients (pts) with solid tumors"), patients were dosed with Et-743 during 3 hour iv infusions every three weeks. Disclosed dosages include 1000, 1300, 1500, and 1650 $\mu g/m^2$ of Et 743. One patient with relapsed metastatic leiomyosarcoma previously treated with chemotherapy and pelvic radiation therapy had a complete remission. Therefore, at least claims 15-17 and 26-29 are entitled to the priority date of GB 9918534.0.

With regard to 9927106.6, filed November 16, 1999, the disclosure indicates infusion times of up to 24 hours, 2-12 hours, 12-24 hours, 2-6 hours, and 3 hours are disclosed on page 2. Intervals of 2 to 4 weeks are disclosed on page 3. Disclosed dosage includes 1500 $\mu g/m^2$ of Et 743 on the page entitled "Ecteinascidin-743 (ET-743) in heavily pretreated refractory sarcomas: early results of the French experience". Four partial responses, 3 minor responses, and 7 disease stabilizations were reported. Therefore, at least claims 27-29 are entitled to the priority date of GB 9927106.6.

Rejection Under Provisional Obviousness Double-Patenting

Claims 12-17 and 24-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending U.S. Patent Application Serial No. 10/492,320. Because the rejection is provisional, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that

> rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

Claims 12-17 and 24-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending U.S. Patent Application Serial No. 10/579,251. Because the rejection is provisional, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 12-17 and 24-35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite due to the term "about" in the phrase "at a dose level of about 500 to about 1650 micrograms/m2 body surface area" in claim 12. Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 12 is amended to remove the term "about" from the indicated phrase. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Applicants thank the Examiner for the withdrawal of the rejection of claims 12-22 under 35 U.S.C. § 103(a) for being unpatentable over Taamma et al. (Eur. J. Cancer) in view of

Barrera et al. (Proceedings of the American Association of Cancer Research) (see Office Action, page 5, lines 1-4).

Claims 12-17 and 24-35 are rejected under 35 U.S.C. § 103(a) for being unpatentable over both Taamma et al. (Eur. J. Cancer) and Cvitkovic et al. (ASCO Meeting held May 17, 1999, Abstract published in Clinical Cancer Research and on-line at www.asco.org) in view of Goodman & Gilman. Applicants traverse the rejection based on the combination of Taamma, Cvitkovic, and Goodman&Gilman. Applicants note that they believe the ASCO Meeting cited with regard to the Cvitkovic reference was held May 15-17, 1999.

Applicants traverse the inclusion of the Cvitkovic reference on the basis that it is not available as prior art against at least some of the claims. As indicated above, Applicants note that GB 9911183.3, filed May 13, 1999 includes an Example disclosing that 10 patients received a dose of 1500 $\mu g/m^2$ of Et 743 as a 24 hour continuous infusion every three weeks, with two partial responses, two minor responses, and three stabilizations. In addition, GB 9911346.6, filed May 14, 1999 includes an Example disclosing that patients received doses of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour continuous infusions, and partial responses, a minor response, and stabilizations were observed. Therefore, the Cvitkovic reference is not available as prior art against at least some of the claims and the rejection should be withdrawn.

In addition to the benefit of the priority dates to which Applicants are entitled, Applicants refer to the attached Declaration of Jose Jimeno Under 37 C.F.R. § 1.131. As indicated by the Declaration, the listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application (M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain) either did not arrive at the subject matter relied upon in the Office Action or were working under the direction of one or more of the listed co-authors/co-

inventors (Jose Jimeno, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset) in arriving at the subject matter cited in the Office Action. As a result, the subject matter cited in the Cvitkovic reference originated with, or was obtained from, applicants. Applicants' disclosure of their own work within the year before the application filing date cannot be used against them under 35 U.S.C. 102(a). See *In re Katz*, 687 F.2d 450 (CCPA 1982) and MPEP 2132.01. Because the subject matter cited in the reference was not invented "by another" the Cvitkovic reference is not available as prior art.

As shown above, Cvitkovic is not available as prior art. Without Cvitkovic, the combination of Taamma and Goodman&Gilman does not render the instant claims obvious.

U.S. case law holds that a proper obviousness inquiry requires consideration of three factors: (1) the prior art reference or references must teach or suggest all the claim limitations; (2) the prior art must teach, motivate, or suggest to those of ordinary skill in the art that they should make the claimed invention or practice the claimed method; and (3) the prior art must establish that in making the claimed invention or practicing the claimed method, there would have been a reasonable expectation of success. *See, e.g., In re Vaeck*, 947 F.2d, 488, 493 (Fed. Cir. 1991); *See also* MPEP 2142.

1) Failure of the references to teach all of the claimed elements

Claim 12 includes the element of "administering at a dose level of 500 to 1650 microgram/m^2 of Et 743". Claims 15 and 26 include the subranges of 1000 to 1650 micrograms/m^2 and 1000 to 1500 micrograms/m^2, respectively. Claim 27 requires a dose level of about 1500 micrograms/m^2. The Office Action states that "Taamma teaches cyclic intravenous administration of Et-743 in the treatment of various sold tumors, such as breast or ovarian

cancer, for an infusion time of 24 hours every 3 weeks" (OA, page 5). However, Taamma is limited to phase I clinical study of Et-743 at doses of 50, 100, 200 and 400 micrograms/m^2.

Additionally, Goodman&Gilman does not cure the deficiency of Taamma. Goodman&Gilman is cited for its discussion of dexamethasone as an effective antiemetic in cancer chemotherapeutic regimens. Goodman&Gilman fails to provide any dosing of Et 743. Accordingly, Applicants respectfully submit that neither Taamma nor Goodman&Gilman, alone or in combination, teach or suggest administering at a dose level of 500 to 1650 micrograms/m^2 of Et 743, 1000 to 1650 micrograms/m^2 of Et 743, 1000 to 1500 micrograms/m^2 of Et 743, or about 1500 micrograms/m^2 of Et 743, respectively. For at least the reason that the references cited by the Examiner fail to teach or suggest all the claim limitations, Applicants request that the rejection be withdrawn.

2) Failure of the references to provide motivation

Applicants respectfully submit that combined references, in failing to teach the claimed ranges, thereby also fail to provide motivation for the claimed ranges. The Examiner indicates that one "would have been motivated to seek an optimal dosing regimen with respect to infusion times and intervals of administration through no more than routine experimentation" (Office Action, page 6, 1st full paragraph). Applicants respectfully disagree with the Examiner's characterization of the many variables involved in human clinical trials of potentially toxic compounds to arrive at a pharmacotherapeutic window as "routine experimentation". Even assuming, *arguendo*, that routine experimentation is involved in clinical trials, the courts have commented on "routine testing" as follows:

> Due to the fact that chemistry is still largely an empirical science it is easy to characterize inventions in the chemical field as but the result of "routine testing." It cannot be denied that "routine testing" is an essential part of many inventions in the chemical field. But

> even "routine" testing, whatever that may be, must be guided and directed by the mental concept of the inventor.

In re Fay et al., 347 F2d 597 CCPA 1965). The courts comments with respect to chemistry are even more applicable to biological systems such as human clinical trials. The references cited by the Examiner provide no direction or motivation for choosing which variables of all the multitude of variables should be evaluated, and what ranges should be applied for those variables.

3) Failure of the references to provide reasonable expectation of success

The present invention is directed to a method of treatment of a human patient for cancer comprising administering Et 743 at a dose level of 500 to 1650 micrograms/m^2 body surface area in cycles by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2 to about 24 hours wherein said treatment results in a reduction in tumor size. Even if, *arguendo*, the claimed elements could have been arrived at by testing all possibilities through the Examiner's suggested "routine optimization", there is no reasonable expectation of success in arriving at the above cancer treatment through routine optimization.

Fields such as petroleum refining and catalytic production of chemicals are amenable to routine optimization through varying reaction temperatures, for example. Logically, when one has a chemical process that is shown to work, one can vary the parameters and at some point arrive at a maximum output.

In treating diseases such as cancer, however, the same cannot be said. It is well-known in the pharmaceutical field that drug candidates often fail during clinical trials. Drug candidates can fail for any number of reasons, such as lack of efficacy *in vivo* despite activity *in vitro* or an unacceptably narrow window of therapeutic efficacy when compared to toxicity effects. In other words, lots of drug trials for cancer fail to arrive at the particular dosing regimen

resulting in reduction of tumor size despite the fact that the drugs have entered clinical trials. Routine experimentation is likely to result in a failed drug candidate. If finding an efficacious drug were merely routine based on phase I trials, then many more cancer drugs would be available. In cancer, the end-point of a reduction in tumor size while maintaining acceptable toxicity levels is not guaranteed. Simply put, there is no reasonable expectation that one of ordinary skill in the art will achieve a reduction in tumor size according to the claims based on entry of the drug candidate in Phase I clinical trials. The best that can be said of the cited references is that the end result of tumor size reduction is a desired but in no way certain outcome of their teachings.

In summary, the cited Cvitkovic reference is not available as prior art, and the remaining combination of Taamma and Goodman&Gilman (1) fails to teach or suggest all the claim limitations; (2) fails to teach, motivate, or suggest to those of ordinary skill in the art that they should make the claimed invention or practice the claimed method; and (3) fails to establish that in practicing the claimed method, there would have been a reasonable expectation of success.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105002.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105002.

Respectfully submitted,
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